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# A urinary calcium–citrate index for the evaluation of nephrolithiasis

JOAN H. PARKS and FREDRIC L. COE

*Renal Program, University of Chicago Pritzker School of Medicine, Chicago, Illinois, USA*

**A urinary calcium–citrate index for the evaluation of nephrolithiasis.** We have performed a multivariate analysis of urine abnormalities in patients with calcium oxalate nephrolithiasis, in which effects of gender were also considered. The characteristic of patients that most clearly sets them apart from normal people is a high level of urine calcium for any given level of urine citrate. Other urine measurements cannot improve upon the separation between patients and normals provided by urine calcium and citrate, and their abnormal relationship to each other. Normal women have higher urine citrate and lower urine calcium than normal men or patients of either sex; normal men differ from stone forming men only moderately. Direct measurements of supersaturation are not helpful in distinguishing between patients and normals, once calcium and citrate have been considered. From our analysis, we have derived a new index for evaluating the significance of urine calcium and citrate levels that seems to offer a better basis for clinical diagnosis than criteria presently in use.

This study concerns the evaluation of patients who form calcium oxalate renal stones because of urinary abnormalities due not to systemic diseases but to otherwise benign genetic disorders, habits, and diet [1]. The abnormalities include high urine excretion of calcium [1–10], oxalate [1, 3, 4, 5, 7, 8], and uric acid [11], low levels of protective inhibitors [12–14] including citrate [2, 3], and excessive urine supersaturation [15]. The standard method of caring for this large group of patients, who constitute the majority of calcium oxalate stone formers [1], is to treat each abnormal urine chemistry as a separate disorder using diet or medication [1, 16–18]. In the present study, we have used a multivariate comparison of urine chemistry values in men and women with and without calcium oxalate stone disease to identify the most impressive and uniform of these abnormalities in stone formers, and have found the most important one is an imbalance between calcium and citrate levels.

## Methods

### *Patients and normal subjects*

Two hundred and thirty-five consecutive men and 95 women with calcium oxalate nephrolithiasis were evaluated using our usual laboratory protocol [1, 16] that also included urine citrate and calcium oxalate supersaturation measurements [15]. Their stone disease was not due to any systemic cause such as primary hyperparathyroidism, enteric hyperoxaluria, renal tubular acidosis, sarcoidosis, immobilization, or Paget's disease, nor to drugs such as acetazolamide, vitamin D supplements, glucocorticoid hormones, antacids, or calcium supplements [1, 16]. As expected, their conventional pathogenetic classifications were mainly idiopathic hypercalciuria [16], hyperuricosuria [11], dietary oxaluria [1], a combination of these, or no metabolic disorder. Thirty–three normal men and 27 normal women were chosen for an age range (20 to 55) comparable to the patients, and an absence of any known medical disorder.

### *Laboratory evaluation*

Three 24 hr urines were collected from outpatients eating their usual diet and following their normal habits. A blood sample was drawn, without stasis, between 8 and 9 a.m. at the conclusion of each urine collection. Calcium, phosphorus, magnesium, creatinine, uric acid, sodium, and potassium levels were measured in blood and urine; oxalate, citrate, pH, and supersaturation were measured in urine only. One to three collections were obtained for each normal subject. Thymol was the urine preservative.

Calcium and magnesium were measured by atomic absorption spectrophotometry, uric acid by the uricase method, phosphorus and creatinine by autoanalyser, sodium and potassium by flame photometry, urine oxalate by the zinc reduction method, citrate by the citrate lyase method [19], and supersaturation using the concentration product ratio [15]. In the latter, calcium and oxalate levels were measured in the urine before and after incubation with 10 mg/ml of calcium oxalate monohydrate crystals, at 37°C, for 48 hr—an interval long enough to permit the crystals and the urine to come into equilibrium so that urine calcium and oxalate levels no longer change. The ratio of the calcium oxalate product before to that after incubation, the concentration product ratio (CPR), is a measure of supersaturation. Values above 1 indicate supersaturation in multiples of the solubility limit, values of 1 indicate no net crystal growth, values below 1 indicate undersaturation—dissolution of the preformed crystals.

### *Calculations*

Urine values were measured as concentrations, with the exception of the CPR. We also expressed each as a 24 h excretion rate, and as excretion per g of urine creatinine, k of body wt, or liter of creatinine clearance. Creatinine clearance

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**Table 1.** Selected urinary measurements

| Measurement | Women | | Men | |
|---|---|---|---|---|
| | Patient | Normal | Patient | Normal |
| Volume, *ml/24 hr* | 1370 ± 72 | 1372 ± 136 | 1626 ± 40[b,d] | 1293 ± 84 |
| Weight, *kg* | 66 ± 2[a] | 62 ± 2 | 81 ± 1 | 77 ± 2 |
| Creatinine, *mg/24 hr* | 1194 ± 24 | 1250 ± 40 | 1886 ± 22 | 1876 ± 69 |
| Creat. Cl., *liter/24 hr* | 157 ± 4 | 152 ± 5 | 191 ± 3 | 182 ± 6 |
| Calcium, *mg/24 hr* | 206 ± 9[c] | 125 ± 12 | 254 ± 7[c] | 181 ± 14 |
| Calcium, *mg/liter* | 171 ± 8[c] | 105 ± 11 | 168 ± 4 | 157 ± 14[d] |
| Oxalate, *mg/24 hr* | 29 ± 1[a] | 25 ± 1 | 39 ± 1[b] | 33 ± 2 |
| Oxalate, *mg/liter* | 23 ± 1 | 22 ± 2 | 25 ± .4[d] | 28 ± 1[e] |
| Citrate, *mg/24 hr* | 551 ± 24[b] | 729 ± 47 | 516 ± 15 | 547 ± 31 |
| Citrate, *mg/liter* | 463 ± 24[b] | 652 ± 71 | 349 ± 11[b,e] | 473 ± 37[e] |
| Uric Acid, *mg/24 hr* | 557 ± 13[a] | 520 ± 21 | 740 ± 11 | 699 ± 33 |
| Uric Acid, *mg/liter* | 472 ± 18 | 484 ± 50 | 502 ± 11[b] | 597 ± 37[d] |
| Un. Uric Acid, *mg/liter* | 101 ± 8 | 113 ± 23 | 99 ± 5 | 122 ± 18 |
| pH | 6.01 ± .04 | 5.98 ± .08 | 6.08 ± .02 | 6.11 ± .08 |
| CPR | 1.64 ± .03[b] | 1.44 ± .06 | 1.70 ± .02 | 1.66 ± .1[d] |
| Sodium, *mEq/24 hr* | 138 ± 5[c] | 109 ± 5 | 189 ± 4[a] | 169 ± 9 |
| Potassium, *mEq/24 hr* | 47 ± 1 | 51 ± 3 | 62 ± 1 | 60 ± 3 |
| Magnesium, *mg/24 hr* | 84 ± 3 | 84 ± 5 | 111 ± 2 | 99 ± 6 |
| Phosphorus, *mg/24 hr* | 773 ± 18[a] | 698 ± 32 | 1055 ± 17[b] | 889 ± 48 |

[a] differs from normal, same sex, $P < 0.05$.
[b] differs from normal, same sex, $P < 0.02$.
[c] differs from normal, same sex, $P < 0.001$.
[d] differs from women, same group, $P < 0.02$.
[e] differs from women, same group, $P < 0.001$.
All values are mean ± SEM. Excretion rates of calcium, oxalate, uric acid, sodium, magnesium, and phosphorus by men exceed those of corresponding women, $P < 0.01$ for all comparisons. Urine calcium and citrate excretion of women and men patients exceeded normal ($P < 0.01$) when expressed per kg body wt, g creatinine, or liter of creatinine clearance (not shown).

was calculated as the ratio of 24 h creatinine excretion to the serum creatinine. Apart from serum creatinine, blood measurements were used here only to guide us in excluding patients with hypercalcemia, and are not analyzed further. The mean value of each urine measurement was calculated for each person, and mean values were taken for subsequent analyses, so each patient and normal contributed only one set of values.

The assembledge of mean values was analyzed using standard methods for digital computer [20]. Simple *t*-tests, and analysis of variance were used to evaluate individual differences between normals and patients. Stepwise discriminant analysis was performed between patients and normals of the same gender. Stepwise partial regression was used to determine predictors of supersaturation in urine of normals and patients. Analysis of covariance was used to ascertain the dependence of calcium excretion upon sodium excretion rate.

**Table 2.** Discriminant analysis of urine chemistry values in normals and patients

| Measurement | Women | | | | Men | | | |
|---|---|---|---|---|---|---|---|---|
| | 0 | 1 | 2 | 3 | 0 | 1 | 2 | 3 |
| Calcium | 15.3 | X | X | X | 0.71 | 4.43 | X | X |
| Citrate | 10.2 | 30.6 | X | X | 13.7 | X | X | X |
| CPR | 9.9 | 3.2 | 6.03 | X | 0.27 | 0.82 | 0.16 | 0.62 |
| Oxalate | 1.2 | 0.26 | 1.54 | 0.06 | 3.97 | 0.34 | 1.31 | 0.002 |
| U. uric acid | 0.45 | 3.4 | 0.05 | 0.37 | 2.15 | 0.26 | 0.92 | 0.12 |
| pH | 0.16 | 0.66 | 0.29 | 0.42 | 0.16 | 0.49 | 0.14 | 1.04 |
| Uric acid | 0.08 | 9.78 | 0.41 | 1.76 | 8.36 | 1.65 | 5.75 | X |
| Volume | 0 | 4.23 | 0.02 | 0.13 | 8.81 | 1.62 | 4.95 | 1.01 |

All values are F statistics. X indicates the variable was used in the discriminant. Numbers above columns indicate the step of the discrimination; at 0, no variable has been chosen; at subsequent steps, the indicated variables have their values set to the grand mean for both groups, and all F values are recalculated.

## Results

### *Individual differences*

Compared to normal, women patients were heavier, their urine contained more calcium, oxalate, sodium, phosphorous and uric acid and less citrate, and was more supersaturated (Table 1). Unlike women, men patients had abnormally high urine volumes (Table 1). Consequently, calcium and oxalate concentrations were not elevated despite hypercalciuria and hyperoxaluria, and uric acid and citrate concentrations were lower than normal despite comparable excretion rates.

### *Discriminant analysis*

Stepwise discriminant analysis (Table 2) identified calcium and citrate concentrations (both sexes), CPR (women), and uric acid concentration (men) as independent abnormalities. At each step, one variable is set to the grand mean of the normal and patient groups combined, and the value of each remaining measurement recalculated for each subject to a new value, using its covariance with the removed variable and the reset value of the removed variable.

Discriminant functions using calcium and citrate distinguished patients from normals very well (Table 3), especially among women. Removal of CPR made almost no difference in

**Table 3.** Correct classification of patients and normals by discriminant functions employing different normalization techniques

| Measurement | Women | | | Men | | |
|---|---|---|---|---|---|---|
| | P | N | B | P | N | B |
| | (95) | (27) | (122) | (235) | (33) | (268) |
| Concentrations | 78(80) | 85(81) | 80(80) | 69 | 58 | 67 |
| mg/24 hr | 77(81) | 85(81) | 79(81) | 56 | 70 | 57 |
| mg/kg body wt | 80(82) | 81(81) | 80(82) | 64 | 70 | 65 |
| mg/g Creatinine | 77(82) | 88(85) | 80(83) | 63 | 79 | 65 |
| mg/liter Creat clearance | 77(80) | 81(81) | 78(80) | 62 | 72 | 63 |
| All[a] | 79(82) | 89(85) | 81(83) | 66 | 75 | 67 |

[a] Used calcium in mg/creat (both sexes), and citrate/creatinine clearance (women) and mg/liter (men); all others used calcium and citrate excretion, directly or normalized as shown. Values are percentages of subjects classified correctly; numbers in parenthesis are when CPR was also available to the program, and was used.

women, and CPR was not used in men. Analyses using excretion rates divided by wt, urine creatinine, and creatinine clearance, were slightly more successful (Table 3) for both sexes. Inclusion of all primary and calculated data led to selection of calcium excretion per g creatinine in both sexes, and citrate excretion per liter of creatinine clearance in women and citrate concentration in men. We chose the discriminant without CPR, and based only on concentrations, as probably best for clinical use in women, as CPR is not widely available, and calculations based on body wt or creatinine excretion or clearance add only marginally to correct selection but considerably to the effort of practical use (Table 3). For men, calcium/g creatinine improved accuracy, and was chosen.

Actual values of urine calcium and citrate from normals and patients create clinical nomograms (Figures 1 and 2) to whose regions urine from stone formers can be compared. The lines of the discriminant functions divide the graphs into normal (upper left) and patient (lower right) zones that are defined not only by actual calcium and citrate levels but by the balance between them; compared to normals, patients of either sex have a lower level of citrate at any particular calcium level. The upward slopes of the discriminant lines, as well as the data themselves make it clear that calcium-citrate balance is more abnormal in patients than are the actual levels of either calcium or citrate, which both overlap normal values extensively.

The discriminant scores derived from citrate and calcium (Fig. 3) are a quantitative diagnostic index. Individual values of the patient scores overlap normal values less than any individual measurements. The score of zero gives the best overall separation of patients from normals, but clinicians may wish to use scores that are more sensitive or more selective, depending upon their goals. Equations for scores in women (Sw) and men (Sm) respectively are: Sw = 0.02053Ca − 0.00548Cit + 0.224; Sm = 0.01489Ca − 0.00336Cit − 0.3491; Cit is urine citrate, mg/liter; Ca is urine calcium, mg/liter in women and mg/g creatinine in men.

It may be that the higher urine volume we observed in our men with stones is not intrinsic to them, but simply results from local treatment practices that somehow influence men, but not women, to drink more water. If so, the discriminant equation based only on urine concentrations of calcium and citrate may be best for men, as it is for women, in clinical settings where the higher urine volume of men patients does not regularly influence results. The equation of score, Sm, in men, based on urine concentrations is: Sm = 0.00624Ca − 0.00461Cit + 0.87922.

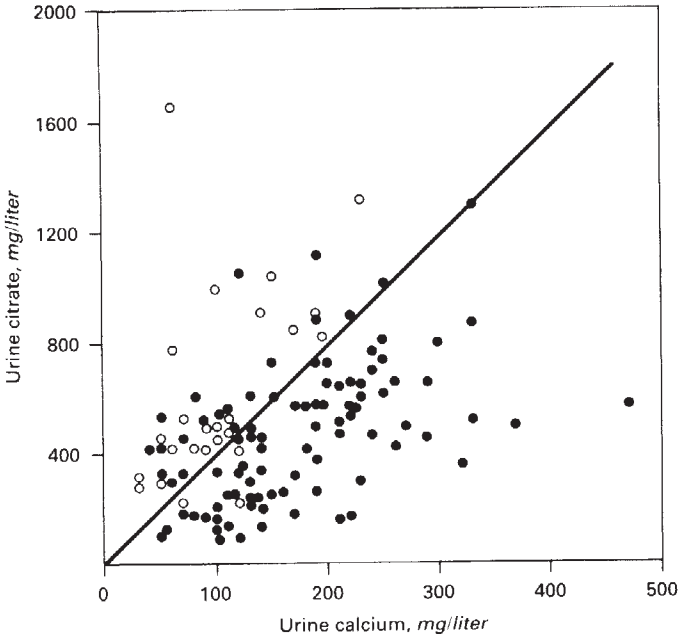


**Fig. 1.** *Urine calcium and citrate concentrations in women with (●) and without (○) calcium oxalate nephrolithiasis.* The line represents the discriminant equation: citrate = 3.746 calcium + 41.1, that gives the best identification of patients and normals (Table 3).

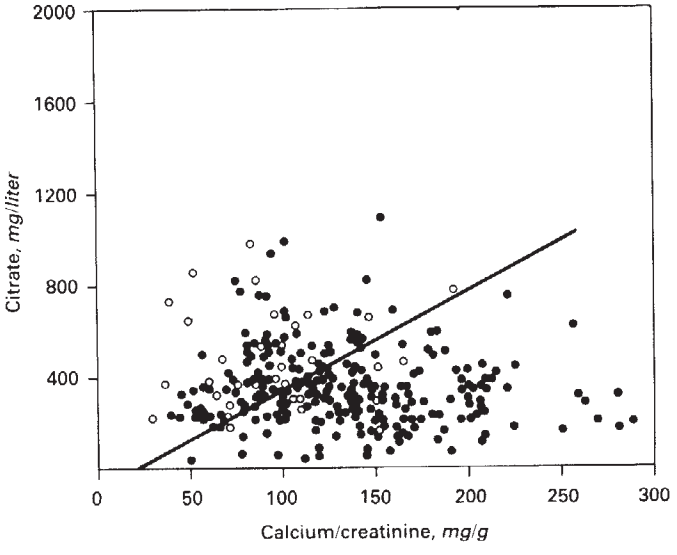


**Fig. 2.** *Urine calcium/g creatinine and citrate concentrations in men with (●) and without (○) calcium oxalate nephrolithiasis.* The line represents the discriminant equation: citrate = 4.432 calcium − 103.9, that gives the best identification of patients and normals (Table 3).

### *Predictors of urine supersaturation*

CPR added little to the discrimination of patients from normals, because it correlated well with other urine measurements (Table 4). Urine oxalate levels were the most important of these and did not differ between patients and normals by very much (Tables 1 and 2). The only differing urine value that also

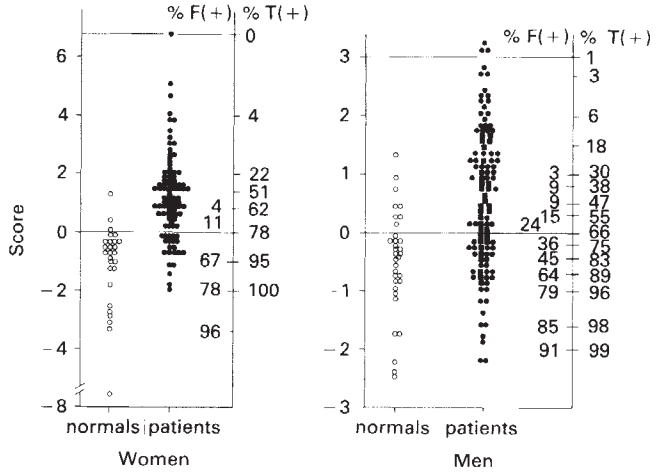


**Fig. 3.** *Discriminant scores for women and men with* (●) *and without* (○) *calcium oxalate nephrolithiasis.* Scores calculated from discriminant equations in text. ■ = 5 cases, rest = 1 case each. Mean values of scores in Table 5.

**Table 4.** Prediction of CPR from urine chemistry values

| Women | | Men | |
|---|---|---|---|
| P | N | P | N |
| Oxalate 0.72 | Oxalate 0.63 | Oxalate 0.56 | Oxalate 0.54 |
| Calcium 0.79 | Uric Acid 0.65 | Calcium[a] 0.60 | Oxalate[a] 0.65 |
| — | Calcium 0.68 | | |

Values are correlation coefficients; chemistry values are concentrations in mg/liter except for [a]mg/24 hr. Successive entries in each column show the stepwise addition of measurements to the predictive regression equation, and the resulting increase in the correlation coefficients.

was correlated with CPR was calcium concentration (in women), which was used in the discriminant score.

### *Effects of treatment on calcium–citrate score*

One way to assess the clinical value of the score based upon calcium and citrate is to measure the score during treatment designed to prevent calcium stone recurrence. We have discussed such treatment, mainly of hypercalciuria and hyperuricosuria, elsewhere [1, 11, 15–17, 36]. In our patients, we have followup data during treatment of 47 women and 114 men that include measurement of urine citrate, and which were obtained during a period in which each patient was entirely free of new stone formation, as judged by the clinical and radiographic criteria we normally employ [1]. Compared to the pretreatment results, scores fell in both sexes (Table 5). However, even though all of the patients were free of new stones, scores were still above those of corresponding normal subjects. In other words, treatment reduced the urine calcium citrate imbalance, but did not fully restore it to normal.

### *Relationship between sodium and calcium excretion*

Because sodium excretion was higher in women patients than normals, and calcium excretion in hypercalciuria is said to reflect a high sodium excretion [21], the relative hypercalciuria of women patients could in part reflect a higher sodium intake. However, the difference in calcium excretion persisted when

**Table 5.** Effects of treatment upon calcium citrate discriminant scores in 47 women and 114 men with calcium oxalate nephrolithiasis

| Sex | Pretreatment | Treatment | Normals |
|---|---|---|---|
| Women | 1.20 ± 0.15 | 0.38 ± 0.2[a] | −1.02 ± 0.3[a,b] |
| Men | 0.48 ± 0.06 | 0.17 ± 0.07[a] | −0.45 ± 0.15[a,b] |

[a] vs. pretreatment, $P < 0.001$; [b] vs. treatment, $P < 0.001$; Mean values ± SEM for pretreatment and normals are for the data detailed in Figure 3; scores were calculated using urine citrate concentration, both sexes, urine calcium concentration in women, and urine calcium per g urine creatinine in men.

the effects of higher sodium excretion were allowed for by analysis of covariance. Sodium and calcium excretions were well correlated: regression coefficient = 0.661 ± 0.157 (SEM) $t = 4.20$, $P < 0.001$. The slopes of the regressions within the two groups were not different ($F = 0.479$), the slopes differed significantly from zero in both groups ($P < 0.0001$), and the means for calcium excretion adjusted for the difference in sodium excretion differed markedly: 202 ± 8 vs. 139 ± 15, patients vs. normals, $P = .0003$. In other words, hypercalciuria could not be accounted for by natriuresis. In men, sodium and calcium excretions also were well correlated: regression coefficient = 0.752 ± 0.103, $t = 7.28$, $P < 0.001$. The slopes of the regressions within the two groups were not different ($F = 0.984$), the slopes differed significantly from zero in both groups ($P < 0.0001$), and the means for calcium excretion adjusted for the means in sodium excretion differed: 252 ± 6 vs. 194 ± 16, patients vs. normals, $P = 0.001$.

### *Comparison between women and men*

Because normal men produce no more urine than women (Table 1) yet excrete more calcium, oxalate, and uric acid, their urine is more concentrated with all three materials, and CPR is higher. Men with stones have higher urine volumes than women, so their high excretion rates do not express themselves in higher concentrations.

The most dramatic differences between genders are best visualized by plotting mean values of urine calcium and citrate concentrations (Figure 4). Normal women stand out as remarkable for their low calcium and high citrate. Normal men and stone forming women resemble one another, whereas men with stones have only slightly higher calcium concentrations, and moderately lower citrate. Put another way, normal men are like women with stones.

## Discussion

Urine calcium and citrate are the two measurements that best distinguish stone formers from normal. Urine volume in men, body wt, uric acid excretion and CPR in women, and oxalate and sodium excretion in either sex are abnormal in stone formers, but are so correlated with calcium and citrate that each adds no independent information with respect to classifying a urine as belonging to a stone former or a normal. If it is true that abnormalities that cause stones are most consistently found among stone formers, then urine calcium and citrate abnormalities appear to play strong and independent roles in producing calcium oxalate stones.

The role of calcium is well known. Over one–half of men and two–thirds of women [18] have normocalcemic idiopathic

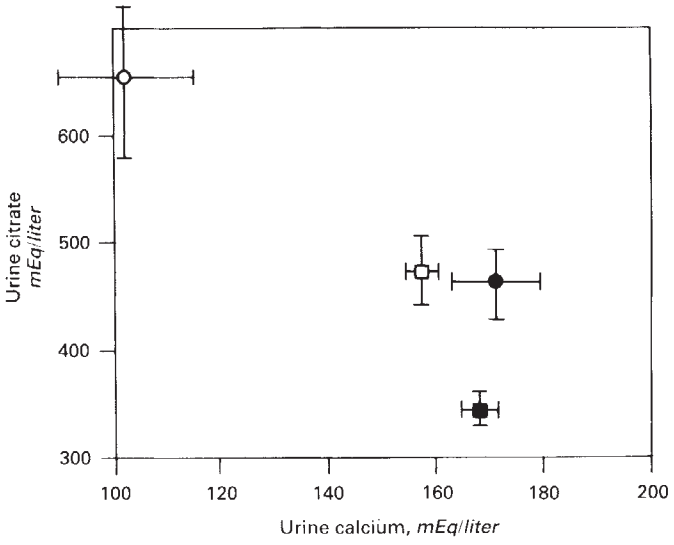


**Fig. 4.** *Urine citrate versus calcium concentration (±SEM) in women (open symbols) and men (closed symbols) with (square) and without (circles) calcium oxalate nephrolithiasis.* Values detailed in Table 1.

hypercalciuria, a familial [22] and probably hereditary [23] trait. Hypercalciuria increases urine supersaturation [15], and high supersaturation promotes crystal formation and growth. Reducing urine calcium with diuretics reduces supersaturation [15] and new stone formation [1, 16].

The role of citrate is less well established. Citrate could be an important natural inhibitor of stone formation, because it slows the growth of calcium oxalate monohydrate crystals at the millimolar concentrations found in urine [24]. Citrate associates with calcium to form a salt that is more soluble than calcium oxalate, and can therefore reduce calcium oxalate supersaturation—by reducing urine free calcium ion concentration—without causing calcium citrate crystallization [25]. Calculations based upon simultaneous consideration of multiple ion associations in a normal urine place calcium citrate at about 45% of the total urine calcium that is non-ionic [25]; since 50% of urine calcium is bound, and therefore non-ionic, low urine citrate could easily increase ionic calcium and, therefore, supersaturation. The fact that it is relatively low in urine of women and men patients supports a role for citrate as a normal protection against stone disease.

That the balance between calcium and citrate is more abnormal in urine of stone formers than urine levels of either substance alone probably reflects the importance of both calcium binding and direct effects of citrate upon crystal nucleation and growth. It may not be so much the absolute urine calcium or citrate levels that determine risk of stone as the relative excess of calcium over citrate. This seems to be the implication of our data, and accords with what is known about the interactions of citrate with calcium and calcium oxalate crystals.

A similar relationship has been described between calcium oxalate supersaturation and total urine calcium oxalate crystal growth inhibition [26]; patients had not only abnormally high urine supersaturation, but a low ratio of inhibition to supersaturation. The nature of the molecules that cause urine crystal growth inhibition is still uncertain; most of the effect is due to molecules larger than citrate, including glycosaminoglycans [27] and a glycoprotein of unusual properties [28]. The important result of this study is that citrate not only provides a context for interpreting the clinical significance of urine calcium levels but is also a well defined molecule whose level in urine can be measured precisely and raised by medical treatment [29].

Gender greatly affects urine chemistry. Normal women seem very different from normal men and from patients of either sex, in having low urine calcium and high citrate. Normal men produce urine like that of stone forming women, and only marginally lower in calcium and higher in citrate than stone forming men. Put otherwise, normal men appear closer to stone forming patients than to normal women, and could be at an intrinsically higher risk for stones. In fact, about 80% of calcium oxalate stones occur in men [18], though men and women are about equal in the population. The urine values of normal women may be the correct "gold standard" for normal, if by normal we mean a low probability of stone. Our findings may partly explain the relative scarcity of calcium oxalate stones in women.

Another striking gender difference is that uric acid excretion of men with and without stones and urine uric acid concentration of normal men exceed that of women (Table 1). Because its volume is high, urine of men with stones does not have a high uric acid concentration. In a subset of patients, mainly men [11], who have urine flow rates that do not exceed normal [11, 30] and elevated urine uric acid excretion rates, urine is more supersaturated with respect to undissociated uric acid than among normal men, and uric acid crystallization is more likely to occur. There is good evidence that uric acid crystals can promote calcium oxalate crystallization [31] and that lowering urine uric acid levels can reduce calcium stone formation in patients with excessive urine uric acid supersaturation [32]. The lack of any detectable independent abnormality of urine uric acid in this study suggests it is a feature of only a fraction of patients, compared to calcium and citrate that seem generally abnormal. However, the uric acid difference between men and women may be another reason why men are more prone to calcium stone disease.

Urine oxalate presents a similar picture. Men excrete more oxalate than women, and have higher concentrations of it that may contribute to their greater propensity to stones. But the differences in calcium and citrate between patients and normals of the same sex so overshadow those of oxalate that oxalate contributes little to differentiating patients from normal, and does not enter our discriminant equations. Nevertheless, in some patients elevated urine oxalate levels may well play a major role in the genesis of stones.

We have tested our calcium citrate discriminant equation during treatment of our patients, mainly with thiazide diuretic agents, allopurinol, and altered diet and fluid intake [1, 11, 15–17, 32]; the score falls towards, but does not reach normal values. Other tests could include an attempt to correlate activity of stone disease with score, but our population is not ideal for that purpose. All of the patients formed recurrent stones before entering our program, and the mean interval between their last new stone and entering the program was about one year, as we have described elsewhere [17]. Another test would be a prospective evaluation of prople who have never formed a

stone, comparing score to eventual stone occurrence; our data do not include such follow-up of our normal subjects.

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*Reprint requests to J.H. Parks, Box 28, University of Chicago Pritzker School of Medicine, 5841 S. Maryland Avenue, Chicago, Illinois 60637, U.S.A.*

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